of small vessel spasm. We also believe that although spasm of resistance vessels may, in certain instances, contribute to the extent of ischemic injury occurring in patients with coronary artery disease experiencing an acute infarction, the evidence is overwhelming that large vessel obstruction is of paramount importance. Thus, while our study does suggest an important independent role of myocardial resistance vessels in the cause of myocardial ischemia and infarction, it does not directly support Hellstrom's interesting but highly speculative hypothesis.

II

Zoneraich raises the possibility of morphologically abnormal arteriolar vessels, as has been described in some, but not all, patients with diabetes mellitus (4,5). The three diabetic patients in our series demonstrated a broad spectrum of coronary flow responses. One patient (Patient 16) demonstrated significant increases in coronary flow without chest pain in the control, cold pressor and ergonovine studies with simultaneous pacing. Patient 17, although demonstrating a normal flow response during the control pacing and cold pressor test studies, was found to have limited vasodilator reserve associated with chest pain and decreased lactate consumption during the ergonovine study. Patient 8 demonstrated limited vasodilator reserve, decreased lactate consumption and chest pain during the control and cold pressor test studies. No other patient in the study demonstrated an elevated fasting blood sugar. Thus, no obvious association between abnormal vasodilator reserve and diabetes mellitus can be made from this small group.

However, the absence of myocardial biopsy information concerning small vessel pathology makes further discussion about the role of fixed small vessel disease speculative only. Two points deserve mention. Another study (6) of patients with chest pain and "normal" coronary arteries in which myocardial biopsies were performed reported no small vessel morphologic abnormalities. Second, fixed small vessel disease in our study would not explain the dynamic features of the coronary flow responses, that is, inappropriate vasodilator reserve or active vasoconstriction unmasked or exacerbated by vasoconstrictor stimuli. The two hypotheses of small vessel disease (fixed versus dynamic) may not be mutually exclusive. Some diabetic patients may have elements of both phenomena.

III

Although we have considered all of Cohn's comments, we have, with great forbearance, limited our response to his questions regarding the science of our study. Cohn expresses concern about the absence of true control subjects in our study (that is, healthy subjects not complaining of chest pain). Ethical considerations prohibit participation of such a population in an extensive invasive study that carries a risk of morbidity and mortality, albeit small. Nonetheless, patients experiencing their typical chest pain during this study clearly differed in their coronary circulatory response to pacing and vasoconstrictor stimuli from those patients not experiencing pain during the study. We believe the patients not experiencing pain can be considered a reasonable control group. Although the number of patients may seem small to Cohn, the demonstration of limited vasodilator reserve, especially when, after ergonovine, there is essentially no overlap of data, was impressive. We have now studied over 50 patients using the same protocol, and the same observations made in our initial study have been noted in this larger group. The hypothesis of abnormal vasodilator reserve of small coronary arteries, presumably arterioles, is reasonably supported by the data, and has been suggested by others (6). Our study shows that this abnormality is dynamic and may be unmasked or exacerbated by vasoconstrictor stimuli. That our findings are biologically significant is strongly suggested by the observation that vasoconstrictor stimuli not only produce the patient's typical chest pain, but that the pain is associated with limitation of coronary blood flow and abnormal lactate metabolism.

Cohn, in his remarks, implies the obvious: that studies should not be published until they satisfy the criteria established for good science. The perception of what these criteria are may vary from one scientist to another, and we cannot bear responsibility for other studies on atypical chest pain to which Cohn refers and which have not withstood the test of time. However, it is our opinion (and that of two reviewers, the editors of JACC and the authors of an editorial accompanying our study) that our findings are important and merit publication.

More studies are clearly needed to clarify the mechanism of angina in these patients. For the present, "small vessel spasm" and "inappropriate small vessel vasodilator reserve" must be considered tentative hypotheses. We hope our work will stimulate further investigation in this possibly common and important manifestation of angina pectoris.

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References

1 Hellstrom HR The injury-spasm (ischemia-induced hemostatic vasoconstrictive) and vascular autoregulatory hypothesis of ischemic disease Am J Cardiol 1982;49 802–10.

2 Berne RM, Rubio R. Coronary circulation In Berne RM, Sperelakis N, Geiger SE, eds Handbook of Physiology The Cardiovascular System Baltimore: Williams & Wilkins, 1979 873–952

3 Maseri A, Severi S, DeNes M, et al "Variant" angina, one aspect of a continuous spectrum of vasospastic myocardial ischemia Am J Cardiol 1978;42.1019–33

4 Blumenthal HT, Alex M, Goldenberg S A study of lesions of the intramural coronary artery branches in diabetes mellitus Arch Pathol 1960;70 27–42

5 James TN Pathology of small coronary arteries Am J Cardiol 1962,20 679–91.

6 Opherk D, Zebe H, Weihe E, et al Reduced coronary dilatory capacity and ultrastructural changes of the myocardium in patients with angina pectoris but normal coronary arteriograms. Circulation 1981.63 817–25

Anterior Transmural Myocardial Infarction: Controlled Randomized Studies

DeWood and colleagues (1) have contributed a technically excellent, well written and therapeutically promising study of surgical reperfusion during acute myocardial infarction. While the authors did not begin scientifically—with an appropriately designed, randomized trial (2)—they have made two separate declarations (both on page 1232) indicating 1) that they understand that uncontrolled, nonrandomized studies could introduce bias, and 2) that "a con-

trolled and random trial will be necessary to form firm conclusions." Time would have been saved and the wished for firm conclusions could be at hand, had the authors begun with a randomized trial (2). Perhaps "better late than never" is what we may anticipate—if these statements are more than ritualistic adornments. (Similar calls for appropriate trials, perhaps to achieve "revision accepted" when the principle may not be accepted, have become commonplace (3). The authors are the most experienced people in this promising field and it would be encouraging to hear from them if they are now, or will be, engaged in a controlled trial. Indeed, 4 years ago, concluding a 387 patient study ("revision accepted July 16, 1979"), they declared, "Although the data are promising, a controlled randomized trial will be necessary to resolve this issue" (4).

I should also like to ask the authors how they determined that they were dealing with *transmural* infarctions. I believe a mass of evidence indicates fairly conclusively that the electrocardiogram is not an adequate guide to that determination (5,6).

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References

1 DeWood MA, Heit J, Spores J, et al Anterior transmural myocardial infarction effects of surgical coronary reperfusion on global and regional left ventricular function. J Am Coll Cardiol 1983;1:1223–34.

2. Spodick DH Randomize the first patient scientific, ethical and behavioral bases Am J Cardiol 1983;51:916–7

3 Spodick DH The randomized controlled clinical trial: scientific and ethical bases Am J Med 1982;73:420–5

4 DeWood MA, Spores J, Notske RN, et al Medical and surgical management of myocardial infarction. Am J Cardiol 1979;44 1356–64

5 Phibbs B "Transmural" versus "subendocardial" myocardial infarction an electrocardiographic myth J Am Coll Cardiol 1983;1:561–4

6 Spodick DH Q-wave infarction versus S-T infarction Nonspecificity of electrocardiographic criteria for differentiating transmural and nontransmural lesions Am J Cardiol 1983;51:913–5

Reply

Spodick suggests that there is somehow a link between a call for controlled randomized trials and the ability to publish in the *Journal of the American College of Cardiology* and the *American Journal of Cardiology*. Since the articles he references did suggest it would be helpful to conduct such trials, he implies that perhaps this was less than a sincere approach to evaluating the problem of reperfusion in myocardial infarction.

I think it is important to understand clearly that those calls for randomized trials were sincere. Publication of the articles was not tied to a requirement that randomization be suggested. The original drafts contained that concept. In no way did the hope of publication nor did the referees require a call for randomization between conventional therapy and reperfusion.

More than 2 years ago, our group voted to begin randomized trials with reperfusion. The institutional review boards of both medical centers approved the randomized trials. It has been difficult to begin these trials, because of difficulty in funding and because of the position taken by the administrators of both medical centers that the trials should be totally funded.

We have therefore entered into a difficult situation wherein the physicians believe that randomization should take place and yet funding and administrative difficulties have hindered progress in that area. Importantly, we have not found the private practice of medicine to be an impediment to the community's acceptance of randomization. None of our practitioners were threatened by the possibility of changing referral patterns because of randomization since the cardiologists and the surgeons in the community who practice invasive cardiology were supportive of the study.

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Correction

In the article, "Noninvasive Evaluation of Normal and Abnormal Prosthetic Valve Function" by Kotler et al. (J Am Coll Cardiol 1983;2:151–73), Figure 4 on page 157 was published incorrectly. The schematic diagrams of the phonoechocardiograms in this figure were reversed. The diagram at the top should have appeared at the bottom, and that at the bottom at the top.